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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,454	03/22/2005	Augustinus Bader	LORWER P33AUS	7961

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DAVIS & BUJOLD, P.L.L.C.
112 PLEASANT STREET
CONCORD, NH 03301

EXAMINER	
FORD, ALLISON M	
ART UNIT	PAPER NUMBER
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,454	BADER, AUGUSTINUS	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87-112* is/are pending in the application.

4a) Of the above claim(s) *100-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-99* is/are rejected.

7)☒ Claim(s) *87 and 96* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

Applicant's Request for Continued Examination filed 8 January 2007 has been received and entered into the case. Claims 87-112 have been added. Claims 1-86 have been cancelled. Claims 87-112 remain pending, with claims 100-112 being withdrawn from consideration. Claims 87-99 have been considered on the merits, as far as they read on the elected species: "hydrogel" as the boundary layer material; and "lipid layer" as the intermediate layer material. All arguments have been fully considered; each argument will be addressed below, as appropriate. Rejections/objections not repeated below have been withdrawn.

Claim Objections

The new claims have addressed the causes for objections previously set forth. However, the following minor informalities are found with the following new claims:

In claim 87, the 1st through 2nd lines (preamble) should read, "...for replacement of a human body part, ..."

In claim 87, the 11th line (step (d)) should read, "...cells in said porous support structure;..."

In claim 96, in line 5 (step (a)) "replaced" is misspelled.

In claim 96, in line 9 (step (d)) "cells" is misspelled.

In claim 96, in line 11 (step (d)) "to the" is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The new claims have addressed many of the causes for rejection previously set forth. However, the new claim language has necessitated the following new grounds of rejection:

Claims 87-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 87 and 96 are rejected as failing to particularly point out and claim the invention. Specifically, based on the specification, and the remarks made in the response received 8 January 2007, it appears the structural relationship between the boundary layer material and the porous support structure is critical to the success of the method, and recitation of such structural relationship is critical to define the claims over the prior art. It appears from the specification that the boundary layer is intended to be a rigid layer, which does more than just provide a barrier to the liquid cell suspension, but also functions to constrict and maintain the shape of the developing tissue, like an external portion of a mold. The criticality of this element is supported in the arguments made in the response of 8 January 2007, wherein applicants point out that the boundary layer of their invention is distinct from that of Bader '282, because Bader '282 uses a bioreactor which has an expandable film (which acts as a boundary layer) (See Response, Pg. 7). Currently, the claims do not limit the boundary layer material to have any particular retaining properties, though these properties appear to be critical to the claimed invention. Therefore the claims are found indefinite for omitting essential elements.

In claim 87, line 8 (step (c)), there is insufficient antecedent basis for the limitation "the living cells" in the claim. It would be remedial to amend the claim to read, " c) introducing living cells into ...."

Furthermore, in claim 87, step (e) is found to render the claim indefinite, as it is not clear when the boundary layer is removed, it appears "after completion of the cell-formation process" refers to the cell growth period recited in step (d), however, it is unclear what "of the implant formed by the cells" refers to? It is not clear if this should be read, "removing the boundary layer after completion of the

implant formed by the cells", if so, the remainder of the step does not correlate, as the step continues to state only after removal of the boundary layer is the implantable tissue formed. Clarification is required.

In claim 94, line 5, there is insufficient antecedent basis for the limitation, "one of the implant and prosthesis", the parent claim has been changed to recite "an implantable tissue construct", thus it appears line 5 should read, "..following production of the implantable tissue construct." Examination has been conducted as such.

In claim 98, it is unclear how vascularizing the porous support structure or prevascularizing the porous support structure functions to remove the boundary layer from the implantable tissue construct. It also remains unclear what "prevascularizing" means (it is not clear what 'prevascularization' is, and thus it is unclear what steps are involved in prevascularizing the construct). Clarification and/or correction are required.

In claim 99, it remains unclear at what time point the plurality of the porous support structure are to be introduced into a nutrient solution. The claim states the purpose of the introduction into the nutrient solution is to facilitate cell growth, but it is not clear if this is referring to step (d) of promoting cell growth or if such a step is intended to be carried out after removal of the boundary layer, to facilitate further cell growth within the tissue construct.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 61-64, 66, 68 and 70-72 have been cancelled, thereby rendering the rejection of those claims moot; however, new claims 87-90, 92 and 94 are substantially similar to claims 61-64, 66 and 68, and thus the rejections of record are now applied to these claims.

Applicants have argued that the method of Bader (WO 01/09282, hereafter Bader '282) & the bioreactor taught therein are intended to solve a different problem than the bioreactor used in the current method. Applicant further argues that the bioreactor used in the method of Bader '282 structurally differs from the bioreactor of the instant claims, and that there is no motivation or suggestion to modify it to be like the bioreactor disclosed in the specification. Specifically applicants point out that in the bioreactor of the current application the porous support structure is the cell culture chamber, whereas the bioreactor of Bader '282 is considered the space between the films. Applicants further point out that the bioreactor of Bader '282 has a flexible exterior wall, which is different than the presently claimed boundary layer. Still further, applicants point out that in the method of Bader '282, while an extracellular matrix may be placed within the cell chamber space, Bader '282 does not describe applying the boundary layer directly to the exterior of the porous support material so as to encompass or enclose the support material entirely within a contiguous outer boundary layer, rather in Bader '282 two separate films, bound together at the periphery by a carrier plate

Applicant's arguments have been fully considered, and are found persuasive in part.

Initially, to address applicants argument that the method of Bader '282 is intended to solve a different problem than that of the instant invention, and that there is no motivation to modify the method of Bader '282 to arrive at the instant invention, it is respectfully submitted that while Bader '282 may set out to solve a different problem than the instantly claimed method, the method of Bader '282 is still substantially the same as the instant method, differing only in that Bader '282 does not specifically

disclose removal of the films (boundary layers) at the end of the culture process to obtain the tissue thereby produced. The rejection of record clearly sets forth that one of ordinary skill in the art would have had proper motivation to remove the films of Bader '282 in order to recover the tissue for further use. One would have had a reasonable expectation of successfully removing the films from the tissue because Bader '282 discloses the films are removable and/or dissolvable (See Bader, Pg. 14, ln 14-21). It has been held that reason or motivation to modify a reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972). Therefore, though Bader '282 does not seek to solve the same problem as the instant application, the method disclosed in Bader '282 renders the current method obvious.

Applicant's arguments which point out structural differences between the bioreactor of Bader '282 and the instant invention are also noted. However, it is respectfully submitted that many of the significant structures or structurally differences on which applicants rely, are not in the independent claims, and thus applicant is relying on elements which are not claimed.

Regarding the argument that the extracellular matrix is not the cell culture chamber, per se, but rather the cell culture chamber is the entire space between the films, it is respectfully submitted that applicants are reading limitations into the claims which are not there. Specifically, the instant claims utilize a bioreactor that comprises a porous support structure encompassed within a boundary layer material, wherein culture medium exists between the porous support structure and the boundary layer material; in the instant case applicants are limiting the cell culture chamber to include only the porous support structure, not the entire space within the boundary layer material. In contrast, in the disclosure of Bader '282, an extracellular matrix (equivalent to the porous support structure) is enclosed between two films (which make up a boundary layer), cell culture medium filling the space between the extracellular

matrix and the films; however, in the case of Bader '282, applicants are defining the cell culture chamber as the entire space within the films (boundary layer). It is respectfully argued that applicants are applying an unfair standard, as the two bioreactors are identical. It is recommended applicants more clearly define the bioreactor in the claims, so as to more specifically and precisely differentiate the bioreactor of the current method from that of the prior art.

Regarding the elastic property of the films in Bader '282, it is noted that the current claims do not in any way exclude or prevent the boundary layer from being elastic in nature, or require it to have a rigid structure.

Regarding the method by which the boundary layer is applied to the porous support structure, neither independent claims 87 or 96 require the boundary layer material to be applied directly to the porous support structure, nor do they describe the structural relationship the boundary layer material must have with the porous support structure once applied, but rather only require the porous support structure to be encapsulated or encompassed by the boundary layer material. In giving this limitation its broadest reasonable interpretation, the method of Bader '282 which states insertion of the extracellular matrix in between the films is considered to read on 'encapsulating the entire porous support structure'. Therefore, the method of Bader '282 is still considered to read on the method as claimed.

Finally, regarding the requirement that the boundary layer be a contiguous layer (e.g. not two separate films joined by a carrier plate), it is respectfully pointed out that only independent claim 96 requires such, claims 87-95 do not preclude the boundary layer from comprising multiple films or pieces of material, and thus the argument is not persuasive with regards to claims 87 and dependents thereof. However, because claim 96 does require the boundary layer to consist of a single, contiguous sheet, the rejection is not maintained against claim 97 or dependents thereof.

Claims 87-90, 92 and 94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bader (WO 01/09282) (translation provided for US national stage application 10/048,440 replied upon for English version- pages cited are those of application 10/048,440).

Bader teaches a cell culturing device and a method of culturing cells on said device to produce a tissue construct which can be in a desired shape. The cell culture device of Bader comprises a support, such as a cell carrier plate; a carrier film laid directly on the support; and a flexible plastic cell-culture film that is attached at the edges to the carrier plate and/or carrier film so as to form a cell culture chamber between the two films (See Bader, abstract). The cells may be cultured directly in the cell culture chamber on the films or an extracellular matrix may be placed in the interior of the cell culture chamber to provide a substrate for the cells (See Bader, Pg. 11, ln 7-19).

In comparing the method of Bader (WO 01/09282) to the instant invention, the extracellular matrix is considered to read on the 'porous support structure'; the films are considered to read on the 'boundary layer' which surrounds the extracellular matrix (porous support structure). The extracellular matrix (porous support structure) can comprise collagen (See Bader, Pg. 14, ln 26-36) or tricalcium phosphate (See Bader, Pg. 11, ln 14-19), both are porous materials which are permeable to the cells and can be degraded or absorbed by the cells (which applicant calls biologically converting the support structure). The cell carrier and/or cell culture films (boundary layer) may be gas-permeable (See Bader, abstract); furthermore because the films form the cell culture chamber, both films (which make up the boundary layer) must be impermeable to cells so as to retain the cell culture in the defined area. The films (boundary layer) may consist of PTFE, silicone, polylactide, polyhydroxyalkanoate, or polyhydroxidebutyrates (See Bader, Pg. 18, ln 24-30); such materials are synthetically made from biological materials, thus they are considered both 'synthetic' and 'biological' materials.

The method of cell culture disclosed by Bader (WO 01/09282) comprises introducing cells into the extracellular matrix (porous support structure) which is located within the cell culture chamber formed

by the films (boundary layers), and supplying nutrients to the cells on the extracellular matrix (porous support structure) via inflow and outflow lines; oxygen is supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

In order to more clearly show how the method of Bader reads on the instantly claimed method, each of the claimed steps will be further discussed below:

Regarding the step of forming the inert porous support material into the desired shape, it is noted that Bader teaches the extracellular matrix (porous support structure) can approximate the size and shape of a desired tissue, for example, bone, heart valve or bladder, so that the finished cell culture may be used to reconstruct the desired tissue (See Bader, Pg. 14, ln 9-17); thus it is inherently required that an initial step comprise forming the extracellular matrix material into the desired shape and size.

Regarding the step of encapsulating the entire porous structure by means of a boundary layer of cell-impermeable material, it is noted that Bader teaches the cells are introduced into the extracellular matrix (porous support structure) inside the cell culture chamber (which is formed by the films (boundary layers)); therefore, the extracellular matrix (support structure) is placed within the cell culture chamber formed by the films (boundary layer), and thus the extracellular matrix is encapsulated by the films (boundary layer).

Regarding the step of introducing the cells to the porous support structure, it is noted that Bader teaches inoculating the cells onto the extracellular matrix (porous support material) via inflow and outflow lines (which applicants call inlets) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27).

Regarding the step of promoting cell growth by introducing oxygen and nutrients into the porous structure and allowing cells to consume the nutrients and the oxygen and to grow and conform to the shape and size of the porous support structure, it is noted that Bader teach nutrients is supplied to the cells on the extracellular matrix (porous support structure) via the inflow and outflow lines and oxygen is

supplied to the growing cells through the gas-permeable films (boundary layers) (See Bader, Pg. 16, ln 25-37 & Pg. 5, ln 13-27). Furthermore, it is noted that the nutrient medium is considered to read on the 'intermediate layer', and thus supplying the nutrient media via the inflow and outflow lines is considered to read on the step of supplying an intermediate layer.

Finally, regarding the step of removing the boundary layers, it is noted that Bader teaches the films (boundary layers) are removable, or may be dissolvable, after the cell culture is complete (See Bader, Pg. 14, ln 14-21); however, they do not specifically teach removing the films, and thus differs in this point.

However, it would have been obvious to one of ordinary skill in the art to remove the films (boundary layers) after the cell culture is complete in order to recover and use the tissue construct produced, which has the shape originally provided by the extracellular matrix (porous support structure). One would expect success in removing the films (boundary layer) in order to recover the tissue construct because Bader teaches the films (boundary layer) are removable or dissolvable (Claims 61-64, 66, 68, 70-72). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leon B Lankford, Jr
Primary Examiner
Art Unit 1651